# AMP and adenosine induced dyspnea perception associated to large and small airways dysfunction in asthma

Hagedoorn, Paul

# AMP and adenosine induced dyspnea perception associated to large and small airways dysfunction in asthma


Authors:
Claire A. Cox[a,b]
Ilse M. Boudewijn[a,b]
Sebastiaan J. Vroegop[c]
Siebrig Schokker[c]
Anne J. Lexmond[d]
Henderik W. Frijlink[d]
Paul Hagedoorn[d]
Judith M. Vonk[b,e]
Martijn P. Farenhorst[a]
Nick H. T. ten Hacken[a,b]
Huib A.M. Kerstjens[a,b]
Maarten van den Berge[a,b]

Affiliations:
a. University Medical Center Groningen, Department of Pulmonology, Groningen, The Netherlands
b. University of Groningen, University Medical Center Groningen Research Institute for Asthma and COPD, Groningen, The Netherlands
c. Martini Hospital Groningen, Groningen, The Netherlands
d. University of Groningen, Department of Pharmaceutical Technology and Biopharmacy, Groningen, The Netherlands
e. University of Groningen, Department of Epidemiology, Groningen, The Netherlands

Contact:
c.a.cox@umcg.nl
m.van.den.berge@umcg.nl



The study was supported by a research grant from TEVA pharmaceutical Industries Ltd


## Introduction

Bronchial provocation is often used to diagnose asthma or monitor disease control. Dyspnea perception, however, associates poorly with the induced drop in $FEV_1$. Some subjects perceive dyspnea well before the drop, while others perceive non. This discrepancy may arise from the origin of dyspnea. As a provocation test solely uses the large airways parameter $FEV_1$, although dyspnea is associated with both large- and small airways dysfunction.

## Aims

We explored if induced **dyspnea perception is equal** for nebulized adenosine 5'-monophosphate (AMP) and dry powder adenosine, targeting large and small airways, respectively. Further we investigated if **dyspnea perception associates** better with large or small airways dysfunction.

## Methods

For this study, we used the baseline data of the previously published OLiVIA study[1], in which asthmatics performed an AMP and an adenosine provocation. All 59 subjects performed spirometry, impulse oscillometry (IOS), and Borg dyspnea score, of whom 36 completed a multiple breath nitrogen washout (MBNW). Spearman's correlation analysis was used to associate the change(Δ) in Borg score to the change in large and small airways parameters. To construct a linear multivariate regression model a large and a small airways parameter[2] was selected (lowest p-value) from spirometry and IOS. MBNW was analyzed separately.

## Results

- Provocation with adenosine and AMP evoked a decreases in $FEV_1$ of 23.4±8% and 21.1±8%, respectively. This corresponded with similar levels of induced dyspnea (Figure 1). ΔBorg did not associated with $\Delta FEV_1$ for neither adenosine nor AMP provocation.
- ΔBorg after adenosine provocation associated with a decrease in $FEF_{25}$ (p=0.01), $FEF_{75}$ (p<0.01), and $FEF_{25-75}$ (p<0.01, Figure 2) and in the multivariate linear regression model (Table 2a) a decrease in $FEF_{25-75}$ was independently associated with an increase in Borg.
- ΔBorg after AMP provocation associated univariately with an increased AX (p=0.05) and a decreased $X_5$ (p=0.04, Figure 3), but in the multivariate analyses no independent associations were found between ΔBorg and any large or small airways parameters (Table 2b).

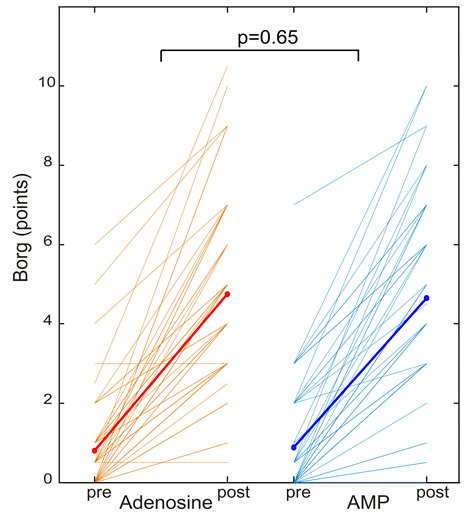


**Figure 1: Changes in Borg score (ΔBorg)** from pre-provocation to post-provocation for adenosine and AMP. Both agents increase dyspnea perception to the same degree.

**Table 1: Baseline characteristics**

| | count or median (IQR) |
|---|---|
| Gender (M-F) | 24 - 35 |
| Age (years) | 47.0 (37.0; 55.0) |
| Smoking (Current-Ex) | 30 - 29 |
| Pack-years (years) | 16.8 (11.0; 26.0) |
| Adenosine provocation (mg) | 3.11 (0.87; 6.38) |
| AMP provocation (mg $mL^{-1}$) | 14.67 (4.7; 44.88) |
| FEV1 (%pred) | 85 (74; 96) |
| FVC (%pred) | 105 (94; 116) |
| $FEV_1$/FVC (%) | 70 (62; 77) |
| $FEF_{25-75}$(%pred) | 49 (35; 65) |
| $R_5$(kPa $sL^{-1}$) | 0.53 (0.42; 0.67) |
| $R_{20}$ (kPa $sL^{-1}$) | 0.42 (0.35; 0.47) |
| AX (kPa $L^{-1}$) | 0.64 (0.24; 1.82) |
| $X_5$(kPa $sL^{-1}$) | -0.13 (-0.22; -0.09) |
| $LCI_{5\%}$ | 6.22 (5.76; 7.37) |
| Scond | 0.04 (0.02; 0.06) |
| Sacin | 0.14 (0.10; 0.19) |

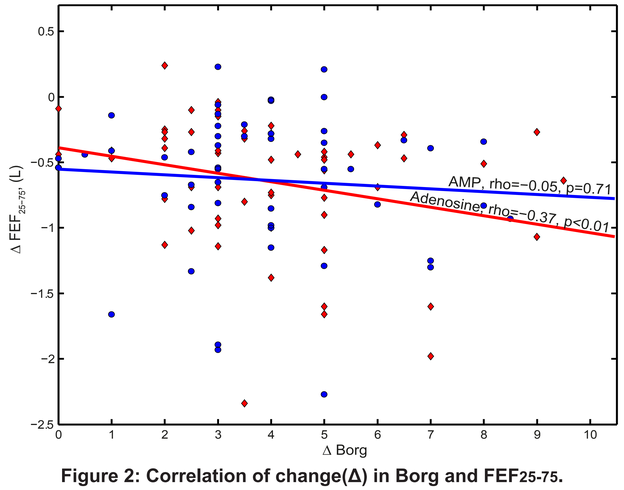


**Figure 2: Correlation of change(Δ) in Borg and $FEF_{25-75}$.** Adenosine(♦) induced **Δ**Borg correlates with **Δ**$FEF_{25-75}$, while AMP(●) induced **Δ**Borg lacks a correlation.

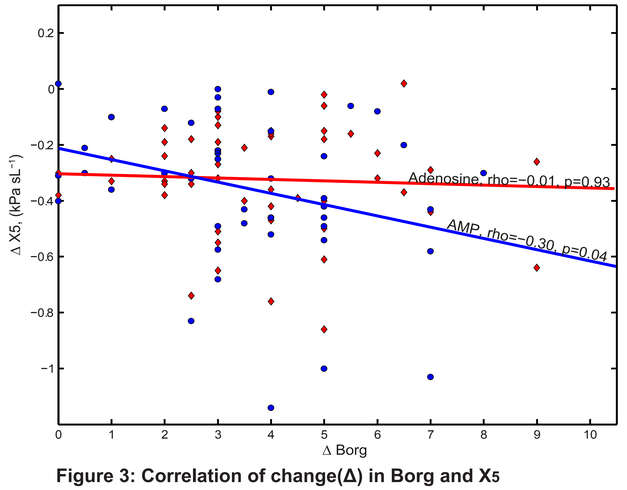


**Figure 3: Correlation of change(Δ) in Borg and $X_5$** AMP(●) induced **Δ**Borg correlates with **Δ**$X_5$, while adenosine(♦) induced **Δ**Borg lacks a correlation.

**Table 2: Multivariate models for ΔBorg**

| | All subjects | MBNW subgroup |
|---|---|---|
| **A. Adenosine** | | |
| | **B (p-value)** | **B (p-value)** |
| Gender | -0.83 (0.37) | -0.81 (0.37) |
| Smoking status | 0.32 (0.65) | 0.45 (0.51) |
| Δ $FEV_1$(L) | 1.50 (0.43) | 0.98 (0.60) |
| Δ $FEF_{25-75}$ ($Ls^{-1}$) | -2.18 (0.04) | -1.82 (0.09) |
| Δ $R_{20}$ (kPa $sL^{-1}$) | -8.28 (0.11) | -6.53 (0.20) |
| Δ $R_5$-$R_{20}$ (kPa $sL^{-1}$) | 2.61 (0.27) | 3.20 (0.18) |
| Δ Scond | | 14.56 (0.16) |
| **B. AMP** | | |
| | **B (p-value)** | **B (p-value)** |
| Gender | 0.25 (0.78) | 0.55 (0.62) |
| Smoking status | -0.11 (0.90) | -0.23 (0.81) |
| Δ $FEV_1$(L) | -0.97 (0.62) | -0.74 (0.72) |
| Δ $FEF_{50}$ ($Ls^{-1}$) | 0.50 (0.54) | 0.60 (0.48) |
| Δ $R_{20}$ (kPa $sL^{-1}$) | -2.00 (0.76) | -1.01 (0.88) |
| Δ $X_5$ (kPa $sL^{-1}$) | -0.64 (0.67) | -0.69 (0.65) |
| Δ $LCI_{5\%}$ | | 0.22 (0.65) |

## Conclusions

- AMP and adenosine induce equally severe dyspnea perception.
- Dry powder adenosine-induced dyspnea seems related to small airways involvement independent of the large airways.
- AMP-induced dyspnea associates with neither large nor small airways dysfunction.
- Our results may indicate that dry powder adenosine and nebulized AMP induce dyspnea via different processes.

GRONINGEN RESEARCH INSTITUTE FOR ASTHMA AND COPD


**References**

1. Cox, C. A. et al. Respir. Med. (2017).
2. Van Der Wiel, E. J. Allergy Clin. Immunol. (2013).